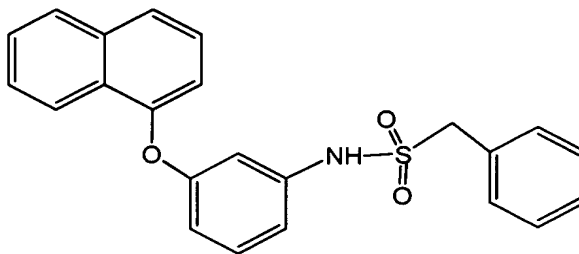


REMARKS

Claims 39-60 are pending. In the present paper, no claims are amended, cancelled, or newly presented for consideration. Thus, claims 39-60 remain pending and under consideration. Claims 39-49 relate to a defined genus of compounds, and claims 50-60 relate to compositions of this genus.

I. The Rejection under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 39-60 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Mittendorf *et al.* (US Patent Nos. US 6,262,112 and US 6,573,278) and International Patent Publication No. WO98/037061. According to the Examiner (*see* Office Action, page 3, item 5), Mittendorf *et al.* and WO98/037061 teach compounds such as:



(*see*, for example, column 13, line 50 of US 6,262,112); where quinoline is allowed for the naphthalene (*see*, for example Table 3, column 51 of US 6,262,112). Further, according to the Examiner (*see* Office Action, page 3, item 6), “[t]he difference between the instantly claimed compounds and the prior art compounds is the attachment between the quinoline and the -O-Phenyl-NH-S(O)₂-Phenyl moiety is through the 5-, 6-, 7- or 8- positions on the quinoline and not the 3-position as instantly claimed.”

The Examiner alleges that it would have been obvious to one of ordinary skill to make quinoline compounds having the same or similar activity as the disclosed compounds wherein the -O-Phenyl-NH-S(O)₂-Phenyl moiety is connected to the quinoline through the 3-position as instantly claimed because “the substitution of one known attachment for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.” *See* Office Action, page 3, item 7.

Applicants respectfully disagree, and respectfully submit that under controlling case law the rejection is legally improper because none of the references cited by the Examiner provide a reason to modify the position of attachment of a quinoline to an -O-Phenyl-NH-

S(O)₂-Phenyl moiety to arrive at the claimed 3-quinolinyl compounds for their indicated uses. *See Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008), and *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350, 1360 (Fed. Cir. 2007).

A. The Proper Legal Standard under 35 U.S.C. § 103 for Compound Claims

The Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103(a). *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). “Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this backdrop the obviousness or nonobviousness of the subject matter is determined.” *KSR*, 127 S.Ct. at 1734, *citing Graham*, 383 U.S. at 17-18. The Supreme Court further noted that within the obviousness analysis, “it can be important to *identify a reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements in a way the claimed new invention does.” *KSR*, 127 S.Ct. at 1741 (emphasis added).

Further, as the Supreme Court in *KSR* explained, an obviousness determination takes into account whether the combination of elements would yield “anticipated success” or “predictable results.” *Id.* at 1739.¹ As such, following the *KSR* decision, the Federal Circuit has based determinations of obviousness on whether a claimed combination would have yielded “predictable results” or whether there would have been “a reasonable expectation of success” in the claimed invention. *See, e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) (patent challenger must show by “clear and convincing evidence” that there would have been a “reasonable expectation of success”); *Aventis Pharma Deutschland GmbH v. King Pharms, Inc.* 499 F.3d 1293, 1301 (Fed. Cir. 2007) (determination of obviousness based on whether the prior art provided an “expectation” that claimed compounds would have the intended properties).

Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can only be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the

¹ The Court also noted that while a showing that a combination was obvious to try “might” be sufficient for a conclusion of obviousness, the Court conditioned such a conclusion on a showing of “anticipated success.” *Id.* at 1742 (emphasis added); *see also* MPEP § 2145 XB.

art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art.

In decisions following *KSR*, the Federal Circuit has affirmed the requirement that obviousness based on structural similarity for chemical compounds must be supported by “identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound...in a particular way to achieve the claimed compound.” *Eisai Co. Ltd. v. Dr. Reddy’s Laboratories, Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008) (citing *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350, 1360 (Fed. Cir. 2007)).

In *Takeda*, the Federal Circuit held that claims to compounds were not found to be *prima facie* obvious over a compound of similar structure because the prior art provided no motivation to modify that compound to arrive at the claimed compounds. *Takeda*, 429 F.3d 1350, 1360. Indeed, the Court noted that in cases concerning structurally similar compounds, the law of obviousness “requires a showing of ‘adequate support in the prior art’ for the change in structure.” *Takeda*, 429 F.3d at 1356 (quoting *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985)).

In *Eisai*, the Federal Circuit held that claims to a specific compound were not obvious over the prior art’s teaching of a structurally similar compound, noting that even post-*KSR*, “a *prima facie* case for obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.” *Eisai*, 533 F.3d at 1359. The Court concluded that “obviousness based on structural similarity can thus be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (*i.e.*, a lead compound) in a particular way to achieve the claimed compound,” (quoting *Takeda*, 429 F.3d at 1356 (quoting *In re Grabiak*, 769 F.2d at 729)) although that motivation need not be explicit in the art. *Eisai*, 533 F.3d at 1357.

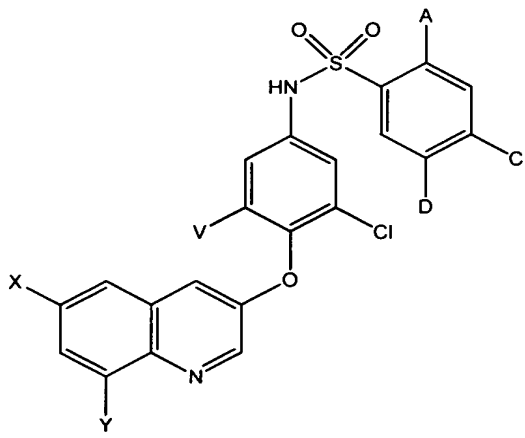
Thus, the Examiner is respectfully reminded that under recent Federal Circuit decisions concerning structurally similar compounds, the law of obviousness requires something more: identification of a reason that would have prompted one of ordinary skill in the art to select and then modify a known compound in a particular way to achieve the claimed compound(s).

Moreover, for purpose of obviousness analysis, a prior art that teaches away negates an obviousness rejection. “[A]n applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect.” *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003) (quoting *In re Malagri*, 499 F.2d 1297, 1303 (CCPA 1974)). “A reference may be said to teach away when a person of ordinary skill, upon reading the reference,... would be led in a direction divergent from that taken by the applicant.” See *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999), quoted by *In re Haruna*, 249 F.3d 1327 (Fed. Cir. 2001).

Turning to the instant case, Applicants respectfully submit that claims 39-60 are not obvious because: 1) a person of ordinary skill in the art, reading the cited references, would not have had a reason to modify the compounds in the cited references to arrive at the claimed 3-quinolinyl compounds; 2) the Examiner has not provided a reason why a person of skill in the art would have selected the compound put forward by the Examiner, and then would have chosen to make the specific modifications to that compound to arrive at the claimed 3-quinolinyl compounds, 3) the cited references teach away from the claimed 3-quinolinyl compounds; and 4) one of ordinary skill in the art would not have had a reasonable expectation that the claimed 3-quinolinyl compounds could be successfully used for their intended purposes.

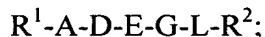
B. A Person of Ordinary Skill in the Art Would Not Have Had a Reason to Modify the Compounds in the Cited References to Arrive at the Claimed Compounds

Pending claims 39-60 recite compounds having the following formula:

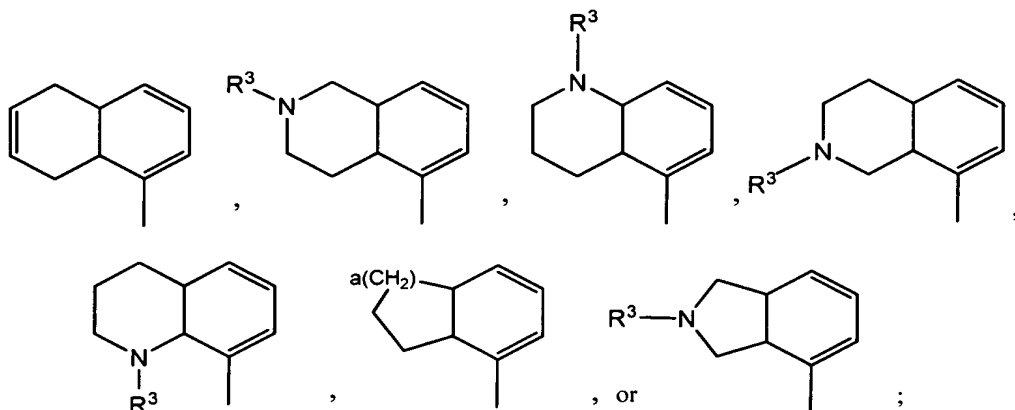


wherein a quinoline is attached through the 3-position of the quinolinyl group to a -O-Phenyl-NH-S(O)₂-Phenyl moiety; wherein the first phenyl group of the -O-Phenyl-NH-S(O)₂-Phenyl moiety (-O-Phenyl-NH-S(O)₂-Phenyl) is di-substituted with a chloro group and substituent V; wherein the second phenyl group of the same moiety (-O-Phenyl-NH-S(O)₂-Phenyl) is directly attached to the sulfonyl on the -NH-S(O)₂- group, and is di- or tri-substituted with substituents A, C and D; and wherein the variables A, C, D, V, X and Y are defined as in the claims. Applicants respectfully submit that Mittendorf *et al.* (US Patent Nos. US 6,262,112 and US 6,573,278) and International Patent Publication No. WO98/037061 provide no disclosure or suggestion of these claim elements.

Mittendorf *et al.* (US Pat. Nos. US 6,262,112 and US 6,573,278) and International Pat. Pub. No. WO98/037061 purport to disclose compounds of the general formula (I):



wherein R¹ represents (C₆-C₁₀)-aryl, quinolyl, isoquinolyl or a radical of the formula;



and wherein A and E are identical or different and represent a bond or (C₁-C₄)-alkylene; D is an oxygen atom or a radical of the formula -S(O)_c- or -N(R⁹)-; G is doubly-bonded (C₆-C₁₀)-aryl or a doubly-bonded optionally substituted 5- to 7-membered aromatic heterocycle; L is -O-, -NH-, -N(R¹⁹)-S(O)₂-, -N(R²⁰)-S(O)-, -N(R²¹)-S(O)₃-, -N(R²²)-S(O)₂-N(R²³)-, -N(R²⁴)-C(O)-, -S(O)₂-N(R²⁵)-, -(O)S(O)₂-, -N(R²⁶)-P(O)(OR²⁷)-, or -N(OH)-S(O)₂-; R² is (C₆-C₁₀)-aryl or an optionally substituted 5- to 7-membered aromatic heterocycle; and the other variables are defined as in the reference. *See*, for example, columns 2-4 of US 6,262,112.

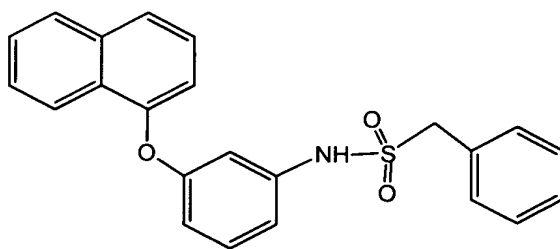
General formula (I) disclosed in the cited references purports to encompass a broad genus of compounds. If all possible embodiments of R¹, A, D, E, G, L, and R² are considered

(ignoring, for example, optional substitutions, length of alkyl chain, and various embodiments of R³, R⁹ and R¹⁹-R²⁷), tens of thousands of compounds are disclosed.

Applicants respectfully submit that Mittendorf *et al.* and WO98/037061 do not provide a reason for one of ordinary skill in the art to select the specific embodiments of R¹, A, D, E, G, L, and R² to arrive at the claimed 3-quinolinyl compounds, because such selection would mean choosing a few combinations from thousands of different combinations. As was the case in *Eisai* and *Takeda*, Mittendorf *et al.* and WO98/037061 do not provide a “finite number of identified, predictable solutions,” but a “broad selection of compounds any of which could have been selected as the lead compound for further investigation.” *Takeda*, 429 F.3d at 1359; *Eisai*, 533 F.3d at 1357. As is well settled, the legally required “reason” to select a species or subspecies from a genus for purposes of 35 U.S.C. §103 does not exist unless there was “[s]ome motivation to select the claimed species or subgenus [from] the prior art.” MPEP § 2144.08. This principle has not changed after the *KSR* decision, as evidenced by the Federal Circuit’s decisions in *Takeda* and *Esai*.

C. The Examiner Has Not Provided a Reason for Modifying the Selected Compound to Arrive at the Claimed Compounds

According to the Examiner, Mittendorf *et al.* and WO98/037061 teach compounds such as:



where “[t]he difference between the instantly claimed compounds and the prior art compounds is the attachment between the quinoline and the -O-Phenyl-NH-S(O)₂-Phenyl moiety is through the 5-, 6-, 7- or 8- positions on the quinoline and not the 3-position as instantly claimed.” See Office Action, page 3, item 6. The Examiner alleges that “it would have been obvious to one of ordinary skill in the art at the time of the invention to make the quinoline compounds connected through another part of the quinoline compound ... because the substitution of one known attachment for another would have yielded predictable results.” See Office Action, page 3, item 7. However, the Examiner has not provided a reason *why*

one of ordinary skill in the art would have been motivated to select the above compound from the tens of thousands of compounds disclosed and the hundreds of compounds exemplified in Mittendorf *et al.* and WO98/037061. Nor has the Examiner provided a reason (other than “predictable results”) why, after selecting that particular compound, one of ordinary skill in the art would have made the specific modifications to R¹, A, D, E, G, L, and R² to arrive at the claimed 3-quinolinyl compounds.

Applicants respectfully point out that the Examiner has the burden of putting forth arguments as to why the claims at issue are obvious. *See KSR, slip op.* p. 15 (“important to *identify a reason* that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does.”); *see also* USPTO Memorandum (“it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.”).

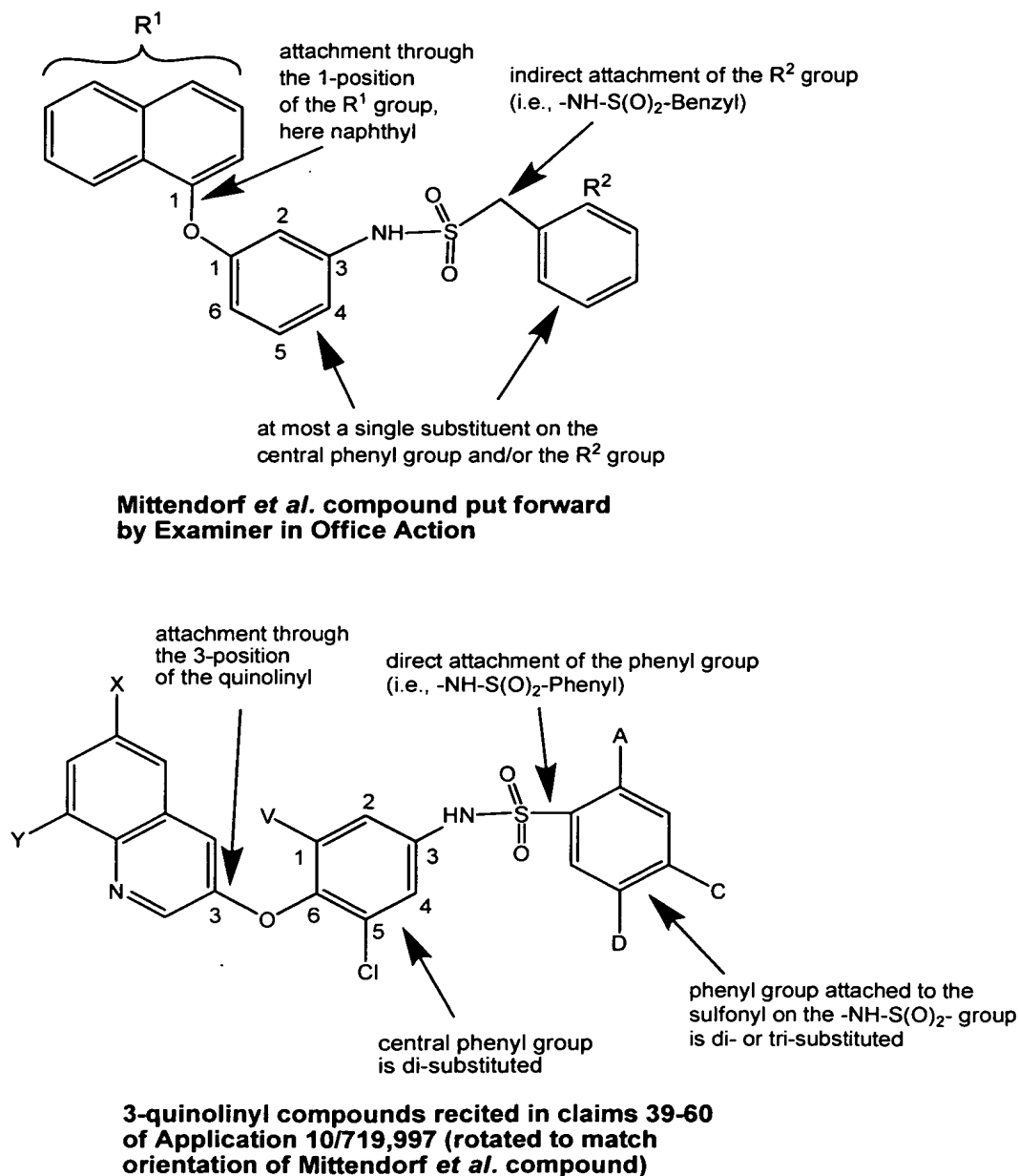
D. The Cited References Teach Away from the Claimed Compounds

Even assuming *arguendo*, that Mittendorf *et al.* and WO98/037061 did provide a smaller selection of compounds, by disclosing, for example, a lead compound (such as the Mittendorf *et al.* compound put forward by the Examiner), Applicants submit that such a selection would not include a quinoline attached through the 3-position to an -O-Phenyl-NH-S(O)₂-Phenyl moiety, because Mittendorf *et al.* and WO98/037061 actually teach away from the claimed 3-quinolinyl compounds.

Mittendorf *et al.* and WO98/037061 purport to teach 33 “very particularly preferred compounds.” None of these 33 particularly preferred compounds disclose: (i) R¹ as quinoline, (ii) attachment of the R¹ group to an -O-Phenyl- moiety through the 3-position of the R¹ group, or (iii) direct attachment of the R² group to the sulfonyl on the -NH-S(O)₂- group (*see*, for example, columns 13-18 of US 6,262,112), as required by the pending claims. Instead, each of the 33 particularly preferred compounds show attachment of the R¹ group (naphthyl or one of the radicals depicted above) to an -O-Phenyl- moiety through the 1-position of the R¹ group, and indirect attachment of the R² group through a -(CH₂)- linker to the sulfonyl of the -NH-S(O)₂- group (*i.e.*, -NH-S(O)₂-Benzyl), as exemplified by the Mittendorf *et al.* compound put forward by the Examiner. *See* column 13, line 50 of US 6,262,112. Further, each of the 33 particularly preferred compounds disclose at most a single substituent on the the central phenyl group and/or the R² group, whereas the pending claims

recite compounds wherein the central phenyl group is di-substituted, and wherein the phenyl group attached to the sulfonyl on the $\text{-NH-S(O)}_2\text{-}$ group is di- or tri-substituted.

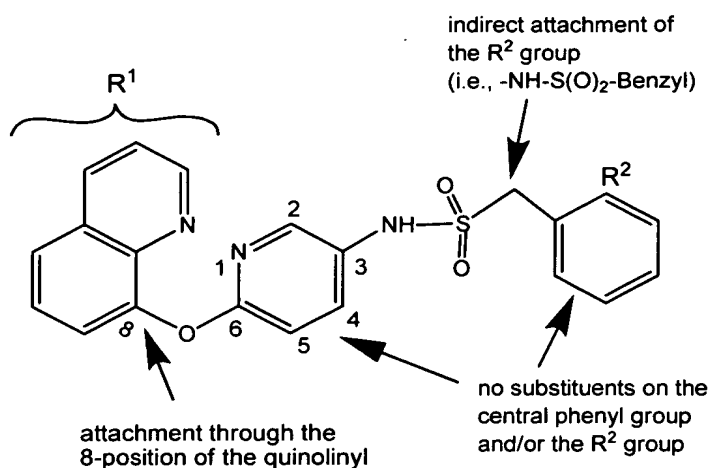
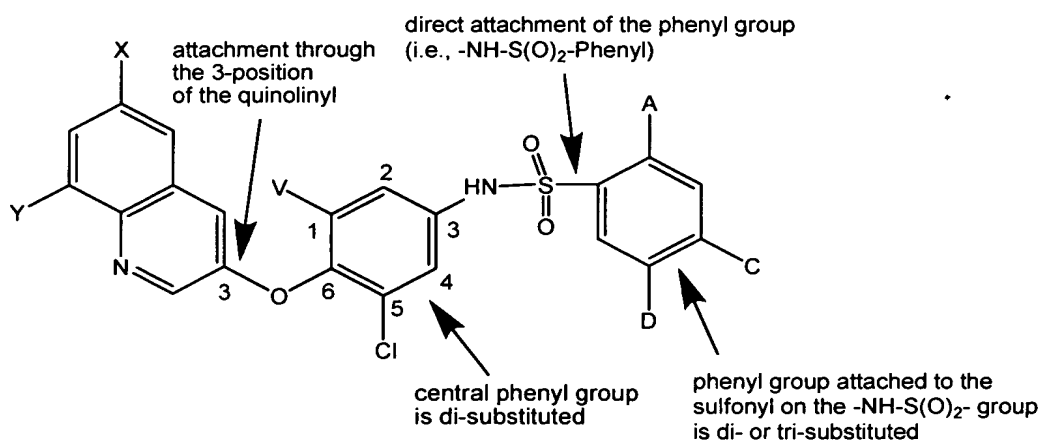
The following Figure shows a comparison of the exemplary Mittendorf *et al.* compound put forward by the Examiner (top) versus the 3-quinolinyl compounds recited in claims 39-60 of the instant application (bottom), highlighting the differences discussed above:



Moreover, of the hundreds of compounds exemplified in Mittendorf *et al.* and WO98/037061, only five compounds disclose R¹ as quinoline. None of these five quinolinyl

compounds disclose (i) attachment of the quinoline group to an -O-Phenyl- moiety through the 3-position of the quinoline group, or (ii) direct attachment of the R² group to the sulfonyl on the -NH-S(O)₂- group, as required by the pending claims. Instead, each of the five quinolinyl compounds show attachment of the quinoline group to an -O-Phenyl- or -O-Pyridyl- moiety through the 8-position of the quinolinyl group, and indirect attachment of the R² group through a -CH₂- linker to the sulfonyl of the -NH-S(O)₂- group (*i.e.*, -NH-S(O)₂-Benzyl). Further, each of the five quinolinyl compounds disclose no substitutions on the central phenyl group and/or the R² group, whereas the pending claims recite compounds wherein the central phenyl group is di-substituted, and wherein the phenyl group attached to the sulfonyl on the -NH-S(O)₂- group is di- or tri-substituted. *See*, for example, compound 40A, columns 107-108 of US 6,262,112.

The following Figure shows a comparison of compound 40A of Mittendorf *et al.* (top) versus the 3-quinolinyl compounds recited in claims 39-60 of the instant application (bottom), highlighting the differences discussed above:

**Compound 40 A of Mittendorf *et al.*****3-quinolinylnyl compounds recited in claims 39-60 of Application 10/719,997 (rotated to match orientation of Compound 40A of Mittendorf *et al.*)**

Applicants submit that one of ordinary skill in the art, reading Mittendorf *et al.* and WO98/037061, would not have had a reason to modify the position of attachment of the quinoline group, the $-\text{CH}_2\text{-}$ linker connecting the R^2 group to the sulfonyl on a $-\text{NH}-\text{S}(\text{O})_2\text{-}$ group, or the number or nature of the specific substituents on the phenyl groups to arrive at the claimed 3-quinolinylnyl compounds, for example, by starting with one of the five 8-quinolinylnyl compounds disclosed in Mittendorf *et al.* and WO98/037061. Applicants submit that one of ordinary skill in the art would instead begin their “reasoned identification of a lead compound” by looking to the 33 particularly preferred compounds, none of which disclose R^1 as quinolinylnyl or the specific attachments or substitutions required by the pending claims.

Applicants further submit that one of ordinary skill in the art, once focused on the 33 particularly preferred compounds, would be taught away from modifying the position of attachment of the R¹ group or the -CH₂- linker connecting the R² group to the sulfonyl on a -NH-S(O)₂- group, because all of the 33 compounds show attachment of the R¹ group to an -O-Phenyl- moiety through the 1-position of the R¹ group, and indirect attachment of the R² group through a -(CH₂)- linker to the sulfonyl of the -NH-S(O)₂- group.

Applicants respectfully point out to the Examiner that a disclosure of a broad prior art genus does not render obvious a claim directed to a subgenus, particularly when that disclosure indicates a preference leading away from the claimed compounds. *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994). Thus, the disclosure of the tens of thousands of compounds in the broad genus of Mittendorf *et al.* and WO98/037061 does not render obvious the claimed 3-quinolinyl compounds of the instant application, particularly when Mittendorf *et al.* and WO98/037061 indicate a preference for non-quinolinyl compounds, wherein the R¹ group (*e.g.*, naphthyl) is attached through the 1-position, and the R² group is indirectly attached through a -(CH₂)- linker to the sulfonyl of the -NH-S(O)₂- group.

E. One of Ordinary Skill in the Art Would Not Have Had a Reasonable Expectation of Success that the Claimed Compounds Could be Successfully Used for their Intended Purposes

The Examiner further alleges that it would have been obvious to one of ordinary skill to make the claimed 3-quinoline compounds “with the reasonable expectation of getting compounds having the same or similar activity ... because the substitution of one known attachment for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.” *See* Office Action, page 3, item 7. However, Applicants respectfully point out that the compounds of Mittendorf *et al.* and WO98/037061 are not alleged to be useful in the diagnosis and treatment of type II diabetes, hypercholesterolemia and inflammatory disorders, as are the claimed 3-quinolinyl compounds. Instead, the compounds of Mittendorf *et al.* and WO98/037061 are purportedly useful in the treatment of neurodegenerative disorders, in particular, cerebral apoplexy and craniocerebral trauma. Therefore, Applicants respectfully submit that it would not have been predictable to one of ordinary skill in the art at the time of the invention that a modification of the compounds of Mittendorf *et al.* and WO98/037061 would have led to a change in indication, for example,

from use in the treatment of neurodegenerative disorders to use in the treatment of, for example, type II diabetes.

Further, the Examiner is respectfully reminded that “[t]he presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds.” MPEP § 2144.09, citing *In re May*, 574 F.2d 1082, 197 U.S.P.Q. 601 (CCPA 1978); *In re Schechter*, 205 F.2d 185, 98 U.S.P.Q. 144 (CCPA 1953). Where the prior art reference neither discloses nor suggests a utility for certain described compounds, the requisite motivation to make the claimed compounds is not present. See *In re Stemiski*, 444 F.2d 581 (CCPA 1971); *In re Lulu*, 747 F.2d 703 (Fed. Cir. 1984). As the Federal Circuit explained in *In re Lulu*:

[A]nalysis of the obviousness or nonobviousness of [the] claimed compounds requires inquiry as to whether there is anything in the [prior art] reference which would suggest the expected properties of the claimed compounds or whether [the prior art reference] discloses any utility ... which would support an expectation that the claimed compounds would have similar properties.

In re Lulu, 747 F.2d 703, 707 (Fed. Cir. 1984).

Returning to the instant case, there is no disclosure in Mittendorf *et al.* and WO98/037061 that would suggest or support an expectation that the modification of the prior art compounds would lead to the claimed 3-quinolinyl compounds with utility in the treatment of type II diabetes or hypercholesterolemia. Therefore, Applicants submit that any presumption of obviousness based on an alleged structural similarity between the prior art compounds and the claimed 3-quinolinyl compounds is overcome.

F. The Rejection Should be Withdrawn

Because neither the Office Action, nor Mittendorf *et al.* and WO98/037061, provide a reason for one of ordinary skill in the art to modify the prior art compounds to arrive at the claimed 3-quinolinyl compounds for their indicated uses, and the cited references, in fact, teach away from the claimed compounds, claims 39-60 are not obvious over Mittendorf *et al.* or WO98/037061.

Accordingly, Applicants respectfully request that the rejection of claims 39-60 under 35 U.S.C. § 103(a) as allegedly obvious over Mittendorf *et al.* (US Patent Nos. US 6,262,112 and US 6,573,278) and International Patent Publication No. WO98/037061 be withdrawn.

CONCLUSION

In light of the foregoing amendments and remarks, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned at (650) 739-3949 if she believes a telephone call could expedite allowance of the instant claims.

No fee is believed due with this response. However, should the Commissioner determine otherwise, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 50-3013, referencing order number 893053-999096.

Date: October 28, 2008

Respectfully submitted,



David C. Pauling

56,056

(Reg. No.)

For: Anthony Insogna (Reg. No. 35,203)

JONES DAY

222 East 41st Street

New York, New York 10017

(212) 326-3939